## REMARKS/ARGUMENTS

Claims 1-8 have been rejected. Claims 3 and 6-7 have been cancelled. Claims 1-2, 4-5, and 8 have been amended to incorporate the limitations of cancelled claims 3 and 6-7 and to specify that the transgenic animal is a homozygous TRAM-knock out mouse. Claims 4 and 5 have also been amended to specify the responses to the TLR4 ligand that are to be measured within the methods of screening, support for which may be found throughout the specification but particularly on pages 5 to 7 of the specification. Accordingly, no new matter has been introduced by way of these claim amendments.

Claims 1-2, 4-5, and 8 are currently pending in the application. Reconsideration of the claims is respectfully requested in view of the following remarks. The Examiner's comments in the Office Action dated May 12, 2008 are addressed below in the order set forth therein.

The Rejections of the Claims Under 35 U.S.C. §101 Should Be Withdrawn

The Examiner has rejected claims 1-8 under 35 U.S.C. §101 because the skilled artisan would not find any of the asserted utilities of the non-human animals to be specific or substantial. As described above, claims 3 and 6-7 have been cancelled. This rejection is traversed as applied to the remaining claims for the reasons provided below.

The Examiner states that although Applicants have provided ample information regarding the phenotypes that TRAM-deficient mice exhibit, "neither the specification nor the art indicates what these symptoms are a disease of" or "that there are TRAM-deficient patients who exhibit these symptoms such that the TRAM-deficient mice can be used as a model of the disease and be used in a screen for medicaments that treat a TRAM deficiency" (Page 4 of the Office Action dated May 12, 2008).

The present invention relates to a non-human animal wherein the function of TRIF-related adaptor molecule (TRAM) genes mediating signaling of Toll-like receptors (TLR) is lacked, especially to a TRAM-knockout mouse that is non-responsive to endotoxin. Endotoxins are released by gram-negative bacteria. When an animal or human has a bacterial infection that is untreated or inadequately treated, the infection can progress to a point where large quantities

of these bacteria are present and produce endotoxins that begin circulating in the blood stream and cause septic shock.

Applicants wish to call the Examiner's attention to U.S. Patent No. 6,660,906 (the '906 patent), which is cited in the concurrently filed information disclosure statement. The utility of the '906 patent is directly analogous to the claims of the present application. The claims of the '906 patent are directed to a transgenic mouse with an endotoxin resistant phenotype produced by a homozygous inactivation of the Tpl2 gene. Several uses for the endotoxin resistant transgenic mice of the '906 patent are provided, including: 1) a method of identifying Tpl2 specific inhibitors of endotoxin shock; and 2) a method of determining whether a compound that is known to inhibit Tpl2 activity *in vitro* also inhibits endotoxin shock *in vivo*. Both methods involve a comparison of wild-type animals to transgenic animals having a functionally disrupted endogenous Tpl2 gene. In both methods, a compound known to induce endotoxin shock is administered to both the wild-type and transgenic animals, along with an experimental agent. Then, in both methods, it is determined whether the wild-type animals show induced resistance to endotoxin shock comparable to that observed in the transgenic animals. Depending on the method, the experimental agent is either a putative Tpl2 inhibitor or a compound that has been shown to inhibit Tpl2 activity *in vitro*. Where the experimental agent is a putative Tpl2 inhibitor, induced resistance to endotoxin shock in the wild-type animals is used to confirm that the experimental agent is in fact a Tpl2 specific inhibitor. Where the experimental agent is a compound that is known to inhibit Tpl2 activity *in vitro*, induced resistance to endotoxin shock in the wild-type animals is used to confirm that the experimental agent also inhibits endotoxin shock *in vivo*.

The '906 patent corresponds to PCT Patent App. Pub. No. 2001/66559, which was published September 13, 2001 and thus forms part of the prior art with respect to the present application. Applicants submit that one of skill in the art would therefore have understood that the phenotype of the transgenic mice of the present invention makes them useful within methods of identifying TRAM-specific inhibitors of endotoxin shock, and/or methods of determining whether a compound that is known to inhibit TRAM activity *in vitro* also inhibits endotoxin shock *in vivo*. The phenotype of the transgenic mice of the present invention has been described

in detail in Applicants' prior response and throughout the specification of the present application. Specifically, as described in the specification, the inventors have performed detailed experiments on responses to TLR4 ligands in TRAM-deficient mice, and have elucidated that: (a) the production of cytokines (TNFα, IL-6, and IL-12p40) of TRAM-deficient mouse derived macrophages was significantly decreased compared to the production level of wild-type macrophages; (b) splenocyte proliferation, and up-regulation of surface molecules were defective; and (c) expression of signaling molecules inducing IFN-beta production was inhibited. Measurement of these responses to TLR4 ligands have been incorporated into the screening methods of claims 4 and 5.

In view of the above discussion, Applicants respectfully submit that the requirements of 35 U.S.C. §101 have been satisfied. Therefore, Applicants request that this rejection be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §112, First Paragraph, Should Be Withdrawn

The Examiner has rejected claims 1-8 under 35 U.S.C. §112, First Paragraph, as failing to comply with the enablement requirement. As described above, claims 3 and 6-7 have been cancelled. This rejection is traversed as applied to the remaining claims for the reasons provided below.

The Examiner states that "the issue at hand relates back to the Utility rejection, wherein the specification does not provide guidance on the specific and substantial use the claimed mice that exhibit the phenotypes described in the specification (see above). Because the specification does not provide guidance [*sic*] a specific and substantial use of the claimed mice, the mice are not enabled" (Page 7 of the Office Action dated May 12, 2008).

As described in detail above, one of skill in the art would have understood that the phenotype of the transgenic mice of the present invention makes them useful within methods of identifying TRAM-specific inhibitors of endotoxin shock, and/or methods of determining whether a compound that is known to inhibit TRAM activity *in vitro* also inhibits endotoxin shock *in vivo*. Because one of skill in the art would have realized that the claimed invention was

useful, they would also have known how to make and use the claimed invention based on the disclosure within the specification.

The Examiner also states that the claims encompass use of knock-out non-human animals other than mouse, but that the specification is not enabling with respect to animals other than mouse. Without acceding to the propriety of this rejection, Applicants have amended to the claims such that they are directed to transgenic homozygous TRAM-knock out mice. Accordingly, this aspect of the rejection has been obviated.

In view of the above discussion, Applicants respectfully submit that the requirements of 35 U.S.C. §112, First Paragraph, have been satisfied. Therefore, Applicants respectfully request that this rejection be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

The Examiner has rejected claims 6 and 7 for indefiniteness on the basis that the claims are drawn to products but depend from method claims. Claims 6 and 7 have been cancelled, as described above. Accordingly, Applicants submit that this rejection has been obviated and request that it be withdrawn.

## CONCLUSION

In view of the aforementioned amendments and remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. §§101 and 112, First and Second Paragraphs, are overcome. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required. However, in the event that extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 C.F.R. §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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